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FOLEY AND LARDNER LLP			OGUNBIYI, OLUWATOSIN A	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/553,904	BJORCK ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 21 October 2005.  
 2a) This action is **FINAL**.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 29-47 is/are pending in the application.  
 4a) Of the above claim(s) 38-47 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 29-47 is/are rejected.  
 7) Claim(s) 29 and 33 is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____ .
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)	5) <input type="checkbox"/> Notice of Informal Patent Application
Paper No(s)/Mail Date <u>3/29/06</u> .	6) <input type="checkbox"/> Other: _____ .

## **DETAILED ACTION**

Claims 29-47 are pending in the application. Claims 29-37 are under examination. Claims 38-47 are withdrawn.

### ***Election/Restrictions***

Applicant's election with traverse of Group I claims 29 to 37 is acknowledged. The traversal is on the ground(s) that Groups III and V are related to Group I and claims 41, 47 and 47 all depend from claim 29 and contain the limitation of Group I and so there is no search burden.

This is not found persuasive because is a national stage of an international application and has been filed under 37 USC 371. Restriction in applications filed under 37 USC 371 are subject to PCT Rule 13.1 and 13.2 and thus search burden is not a criteria for restriction.

The groups of inventions listed in the restriction requirement do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical feature because the technical feature linking groups I-V is an anti-streptococcal agent. This technical feature is not a special technical feature as it does not make a contribution over the prior art in view of Cue et al (PNAS vol. 97: p. 2858-2863, March 2000, cited in IDS) who teaches a non-peptide integrin antagonist that can be used for treatment of streptococcal infections. Thus, Groups I to V lacks unity. Note that claim 41 is drawn to an anti-streptococcal agent irrespective of how said agent is identified i.e. claim 41 is a product by process claim. “[E]ven though product-by-process claims are limited by and defined by the process; determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process

claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” In re Thorpe, 777

F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted)

The requirement is still deemed proper and is therefore made FINAL.

Claims 38-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No.20081004.

***Priority***

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

***Drawings***

The drawings in this application have been accepted. No further action by Applicant is required.

***Information Disclosure Statement***

The information disclosure statement filed 3/29/06 has been considered. An initialed copy is enclosed.

***Claim Objections***

Claims 29 and 33 are objected to because of the following informalities:

Claim 29 step C, the symbol for ‘beta’ is incorrect

Claim 33 line 2, there should be a space between ‘a’ and ‘PMN’. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 29-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for identifying an anti-streptococcal agent, which method comprises: (a) providing, as a first component, an isolated streptococcal M protein or a functional variant thereof; (b) providing, as a second component, isolated fibrinogen or a functional variant thereof; (c) providing, as a third component, an isolated .E-backward..sub.2

integrin or a functional variant thereof; (d) contacting said components with a test substance under conditions that would permit the components to interact in the absence of the test substance; and (e) determining whether the test substance inhibits the interaction between the components; thereby to determine whether a test substance is an anti-streptococcal agent; or which method comprises: (f) providing, as a first component, a streptococcal M protein or a functional variant thereof; (g) providing, as a second component, fibrinogen or a functional variant thereof; (h) providing, as a third component, one or more polymorphonuclear neutrophils (PMNs); (i) contacting said components with a test substance under conditions that would permit the components to interact in the absence of the test substance; and (j) monitoring any inhibition of the activation of PMNs; thereby to determine whether a test substance is an anti-streptococcal agent.

The instant claims require the use of functional variants of streptococcal M protein, functional variants of fibrinogen and functional variants of beta2 integrin. Claims 35 and 36 also requires the use of functional variants or homologues of the M1 protein of *S. pyogenes* such as fragments of functional variants or homologues which retain the ability to form a complex with fibrinogen.

The genus of homologs of the M1 protein is very large and variant. The specification teaches that there are more than 80 different streptococcal M proteins (See p. 7 lines 25 to 31). The genus of functional variants of streptococcal M proteins is very large (over 80 different M proteins) and composed of species with differing structure. The genus of functional variants of all these M proteins comprise species which result from insertions, deletions (fragments) or substitutions in the amino acids sequence of all these streptococcal M proteins. See specification p. 10. The specification provides insufficient written description to support the genus encompassed by the claims since there is no correlation between a common structure of the widely variant species of M proteins and insertion, deletion

or substitution mutants and the required function to form a complex with fibrinogen (specification p. 8 lines 1-3). The genus of fragments and other functional variants of M1 protein of *S. pyogenes* is also large and variant comprising insertion, substitution and deletion mutants. The specification does not set forth the common structure of the genus of fragments and other functional variants of M1 protein that complexes with fibrinogen. The only fragment described that complexes with fibrinogen is and thus leads to mobilization of heparin binding protein is fragment A-S derived from M1 protein (See specification p. 32 lines 19-31).

The genus of functional variants of fibrinogen is very large and composed of species with differing structure as a result of insertions, deletions (fragments) or substitutions anywhere in the amino acid sequence of fibrinogen. The specification requires functional variants of fibrinogen to maintain the ability to bind and thus form a complex with a streptococcal M protein and the complex binds beta 2 integrin. See specification p. 12 lines 30-31. The specification provides insufficient written description to support the genus encompassed by the claims since there is no correlation between a common structure of the widely variant species of functional variants of fibrinogen and the required function to form a complex with M protein. The specification describes a fragment of fibrinogen (SEQ ID NO: 2) that inhibited the aggregation of purified PMNs in a mixture of plasma and M1 protein. SEQ ID NO: 2 is derived from the NH2 terminal region of fibrinogen that contains the binding site for CD11c/CD18 beta 2 integrin. See specification p. 35 lines 30 to p. 31). It is not clear however, whether SEQ ID NO: 2 retains the ability to complex with M1 protein as SEQ ID NO: 2 did not have any effect on the interaction between M1 protein and fibrinogen in a competitive assay (p. 36 lines 21 to 24). Thus, the specification fails to adequately describe which functional variant of fibrinogen or the common structure of fibrinogen

that retains the ability to complex with M1 protein or the genus of streptococcal M proteins set forth above.

Beta 2 integrins are the most abundant integrins expressed by PMNs. They have alpha and beta chains and 4 different alpha chains can associate with the beta chain. See p. 14 lines 28 to 31 to p. 15 lines 1-6. The specification teaches that alphaMBeta2 (CD11b/CD18) and alphaXbeta2 (CD11c/CD18) are the receptors of fibrinogen. The specification requires the functional variant of beta 2 integrins to maintain the ability to bind to streptococcal M protein-fibrinogen complex.

The specification teaches that a functional variant of beta 2 integrin may be any of the alpha chains or any combination of an alpha chain with the beta 2 chain. Specification p. 15 lines 28-30. Also functional variants may be insertion, deletion or substitution mutants of said functional variants. Thus, the genus of functional variants of beta 2 integrin is very large and composed of species with differing structure. The specification does not describe the common structure of this genus that maintains the ability to bind to a streptococcal M protein-fibrinogen complex. Note that the genus of streptococcal M proteins and the genus of fibrinogen that form a complex has not been adequately described as set forth above. The specification only reduces to practice experiments with PMNs which express on their surfaces the intact beta2 integrin. See p. 35 lines 7 to p. 28.

It is known that which changes to an amino acid sequence (deletions, substitutions or insertions or combinations thereof) of a protein that can affect the function of said protein is unpredictable without experimentation or description of which domains are necessary for function e.g. the functional requirements of the proteins set forth above. Even the type of amino acid residue substituted at a particular position in a protein is important for maintaining function of a protein (See Bowie et al. March 1990, Science, Vol. 247:1306-1310 and Lazar et al. Molecular and Cellular Biology March 1988, p. 1247-1252). Therefore, it is unpredictable which

of the functional variants and homologs set forth above will perform the function attributed to them and thus be used to identify an anti-streptococcal agent as there is no common structure of each of the genus described above which correlates to the function ascribed to the genus of the proteins set forth above. For such an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, for example, *Noelle v Lederman*. 355 F. 3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) and *In re Alonso* (Fed. Cir. 2008-1079).

The purpose of the written description requirement is broader than to merely explain how to 'make and use' [the invention] *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991). *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that: ...To fulfill the written description requirement, a patent specification must describe an invention and does so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* 107 F.3d at 1572, 41 USPQ2d at 1966. The instant specification as the time does not provide adequate written description of functional equivalents of fibrinogen that complexes with all M proteins (there are over 80) or functional equivalents of all M proteins and therefore does

not provide adequate written description of said complexes that binds to beta 2 integrin or functional variants thereof and thus, the specification has not adequately described the instant method of identifying an anti-streptococcal agent.

Claims 29-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for identifying an anti-streptococcal agent, which method comprises: (a) providing, as a first component, an isolated streptococcal M protein or a functional variant thereof; (b) providing, as a second component, isolated fibrinogen or a functional variant thereof; (c) providing, as a third component, an isolated .E-backward..sub.2 integrin or a functional variant thereof; (d) contacting said components with a test substance under conditions that would permit the components to interact in the absence of the test substance; and (e) determining whether the test substance inhibits the interaction between the components; thereby to determine whether a test substance is an anti-streptococcal agent; or which method comprises: (f) providing, as a first component, a streptococcal M protein or a functional variant thereof; (g) providing, as a second component, fibrinogen or a functional variant thereof; (h) providing, as a third component, one or more polymorphonuclear neutrophils (PMNs); (i) contacting said components with a test substance under conditions that would permit the components to interact in the absence of the test substance; and (j) monitoring any inhibition

of the activation of PMNs; thereby to determine whether a test substance is an anti-streptococcal agent.

The facts that should be considered in determining whether a specification is enabling or if it would require an undue amount of experimentation to practice the invention include 1) the quantity of experimentation necessary to make or use the invention based on the content of the disclosure, (2) the amount of direction or guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988). The determination that “undue experimentation” would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, the factors that weigh more in making the instant enablement rejection are discussed below.

#### Nature of the Invention/Breadth of the Claims

The instant invention is drawn to identifying or screening for anti-streptococcal agents. Thus, the claims are drawn to identifying an agent that can eliminate any type of *Streptococcus*.

There are many types of *Streptococcus* -e.g. *agalactiae*, *pyogenes*, *pneumoniae*, *equi* to name a few. The claims also requires providing any type of streptococcal M protein or functional variants and providing fibrinogen or functional variants and beta 2 integrin or functional variants

thereof. There are over 80 different streptococcal M proteins (p. 7 lines 25 to 31). The genus of functional variants of fibrinogen and M proteins is very large and composed of species with differing structure as a result of insertions, deletions (fragments) or substitutions anywhere in the amino acid sequence of fibrinogen or M proteins. The specification requires functional variants of fibrinogen and M protein to maintain the ability to bind and thus form a complex with each other and the complex binds beta 2 integrin. See specification p. 12 lines 30-31. Thus, the breadth of the instant claims is extremely broad. Independent claim 29 comprises two methods with different end points. Claims 29 a-e, in step e determines whether the test substance inhibits the interaction between the components; thereby to determine whether a test substance is an anti-streptococcal agent. Claims 29 f-j step j monitors inhibition of the activation of PMNs thereby to determine whether a test substance is an anti-streptococcal agent.

The amount of direction or guidance presented and the presence or absence of working examples, the state of the prior art and the predictability or unpredictability of the art

The specification teaches that neutrophil proteinases releases M1 protein from surface of *S. pyogenes* M1 protein (p. 30); teaches that M1 protein triggers the release of heparin binding protein (HBP) (p. 31); teaches that the release of HBP from PMNs in human blood is modulated by signal transduction mediators and extracellular divalent metal ions concluding that the binding of M1 protein to PMNs is dependent on intracellular and extracellular divalent metal ions (p. 33); teaches that M1 protein precipitates fibrinogen in plasma (p. 34); teaches that precipitates of M1 protein and fibrinogen activate PMNs and teaches that M1 protein induces HBP release is blocked by beta 2 integrin antagonist (p. 35). However, the specification does not correlate the instant method steps with identifying an anti-streptococcal agent.

The specification describes a fragment of fibrinogen (SEQ ID NO: 2) that inhibited the aggregation of purified PMNs in a mixture of plasma and M1 protein. SEQ ID NO: 2 is derived

from the NH2 terminal region of fibrinogen that contains the binding site for CD11c/CD18 beta 2 integrin. See specification p. 35 lines 30 to p. 31). It is not clear however, whether SEQ ID NO: 2 retains the ability to complex with M1 protein as SEQ ID NO: 2 did not have any effect on the interaction between M1 protein and fibrinogen in a competitive assay (p. 36 lines 21 to 24). Even if SEQ ID NO: 2 or other beta 2 integrin antagonists or other test substances inhibits the interaction between the M1 protein/fibrinogen complex with beta 2 integrin or inhibits the interaction of the three components, this does not mean that said test substance is an anti-streptococcal agent. The inhibition of interaction between any M protein/fibrinogen complex with beta-2 integrin at best prevents release of HBP and inflammatory factors that contribute to the pathology seen with *Streptococcus* infection but does not predict that said test substance can also eliminate *Streptococcus*. This is evidenced by the fact that when mice are infected with M1 protein expressing *S. pyogenes* bacteria and are treated with SEQ ID NO: 2, the pathology in the lungs were less affected compared to control, however the mice were still infected with bacteria (no bacteria in blood indicating that the bacteria had not started to disseminate from the site of infection). See specification p. 38 lines 27 to 31 to p. 39. Although, the bacteria shed M1 protein that forms precipitates and causes pathology in the lungs which is less when treated with SEQ ID NO: 2, there is no indication that SEQ ID NO: 2 eliminates the *S. pyogenes* bacteria. Thus, inhibition of activation of PMNs or inhibition of the interaction of M protein, fibrinogen and PMNs or beta-2 integrin by a test substance does not necessarily correlate with elimination of *Streptococcus* but may correlate with reduction in pathology that may be caused by circulating M1 protein/fibrinogen complexes.

The specification does not also correlate identifying anti-streptococcal agents using other M proteins or functional variants thereof and functional variants of fibrinogen and functional variants of beta 2 integrin.

Around the time of filing of the instant application, Herwald et al (Cell, Vol. 116367-379, February 6, 2004, cited in IDS) teaches that the formation of M1 protein/fibrinogen complexes, their interaction with  $\beta_2$  integrins resulting in the activation of PMNs, and the subsequent release of leakage-inducing HBP, represent a chain of events which may explain the extremely rapid progress of STSS (toxic shock syndrome and the severity of the syndrome). The identification of this potentially important patho-physiological pathway and the observation that a peptide interfering with the interaction between fibrinogen and  $\beta_2$  integrins, prevents M protein-induced lung lesions, suggest that the data described here could be helpful in the development of therapeutic strategies in STSS (see p. 377 column 2 second full paragraph). Thus, the results in the specification may predict that beta 2 antagonist (SEQ ID NO: 2) can be used to treat toxic shock syndrome as it relates to M1 protein/fibrinogen complex binding to beta 2 integrin but does not predict that SEQ ID NO: 2 can be an anti-streptococcal agent by eliminating or reducing titers of *S. pyogenes*.

The quantity of experimentation necessary to use the invention based on the content of the disclosure and the relative skill in the art

A significant amount of experimentation would be required of the skilled artisan to screen all M protein and functional variants thereof and all functional variants of fibrinogen and all functional variants of beta 2-intergrin or PMNs with tests substances to determine which test substance inhibits the interaction of the 3 components or inhibit activation of PMNs. Further

experimentation would then be necessary to screen for any test substance that inhibits the interaction of the 3 components or inhibit activation of PMNs for the ability to eliminate any type of *Streptococcus* i.e. screening against all species of *Streptococcus*. Although one of ordinary skill in the art can develop such assays it would require a large amount of experimentation.

In conclusion, in view of the above considerations, undue experimentation would be required of the skilled artisan to make and use the instant invention *as claimed* to identify an anti-streptococcal agent.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 29, 30, 32 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Poirier et al. Infection and Immunity, Jan. 1989, p. 29-35, cited in IDS.

A method for identifying an anti-streptococcal agent, which method comprises: (f) providing, as a first component, a streptococcal M protein or a functional variant thereof; (g) providing, as a second component, fibrinogen or a functional variant thereof; (h) providing, as a

third component, one or more polymorphonuclear neutrophils (PMNs); (i) contacting said components with a test substance under conditions that would permit the components to interact in the absence of the test substance; and (j) monitoring any inhibition of the activation of PMNs; thereby to determine whether a test substance is an anti-streptococcal agent.

Poirier et al teaches a method for identifying an anti-streptococcal agent comprising

- 1) providing a streptococcal M protein via Streptococcus bacteria which expresses M protein on its surface (see fig. 4 p. 32)
- 2) providing fibrinogen via fibrinogen bound to Streptococcus bacteria expressing M protein (fibrinogen bound bacteria) (see p. 31 under 'Fgn-binding assays" and "fluorescence – activated sorting of M positive S. sanguis" and "opsonophagocytic assays)
- 3) providing one or more neutrophils (see p. 32 column 2 last bridging sentence to p. 33 column 1 and table 1 "phagocytosis of M-5 transformed S. sanguis {and S. pyogenes} by human polymorphonuclear leukocytes" and "percentage of neutrophils with associated bacteria treated with preimmune and immune rabbit sera"
- 4) contacting said components in an opsonophagocytic assay with a test substance (anti-pepM5 serum) under conditions that would permit the components to interact in the absence of the anti-pepM5 serum i.e. preimmune serum control (see table 1)
- 5) and monitoring the inhibition of activation of neutrophils via opsonization assay i.e. in the absence of anti-pepM5 serum only 32% or 9% of neutrophil opsonizes S. sanguis or S. pyogenes respectively i.e. fewer neutrophils are activated to phagocytose said bacteria compared to in the presence of anti-pepM5 serum 100% or 91% of neutrophils opsonize are activated to

opsonizes said bacteria. See table. Thus, the phagocytosis of *S. sanguis* or *S. pyogenes* by neutrophils indicate that the anti-pepM5 serum is an anti-streptococcal agent.

As to claims 32 and 34, as evidence by the Berge et al (The Journal of Biochemistry vol. 270 p. 9862-9867, 1995), *S. pyogenes* produces streptococcal cysteine proteinase (SCP) which is cleaves M protein (see p. 9862 column 2 first full paragraph), thus the *S. pyogenes* and *S. sanguis* bacteria in the assay above inherently produce endogenous SCP protease which cleaves surface M protein thus providing M protein.

***Status of the Claims***

Claims 29 and 33 are objected to.

Claims 38 to 47 are withdrawn.

Claims 29-37 are rejected.

***Prior art Made of Record Pertinent to Applicants Disclosure***

Edens et al. Current Opinion in Hematology 2003, 10:25-30 -teaches that azurocidin (also known as cap37 or heparin binding protein)- is released after activation of polymorphonuclear leukocytes, such as after ligation of the major adhesive integrin CD11b/CD18 (a beta 2 integrin). See abstract.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-9939. The examiner can normally be reached on M-F 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Examiner Shanon Foley can be reached on 571-272-0898.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Oluwatosin Ogunbiyi/

Examiner, Art Unit 1645

/Robert B Mondesi/

Supervisory Patent Examiner, Art Unit 1645